REMARKS

Claims 28-61 are pending in the application and have been examined. Claims 28-61 stand rejected. To facilitate prosecution of this application, Claims 30, 49-54, and 59-61 have been canceled without prejudice to applicant's right to prosecute the canceled claims in a subsequent patent application. Claims 28, 29, 31-48, and 55-58 have been amended. Claim 62 has been added. Applicant respectfully requests reconsideration and allowance of Claims 28, 29, 31-48, 55-58, and 62.

The Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

Claims 28-61 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because of the absence of an article in the preamble. Claims 30, 49-54, and 59-61 have been canceled and Claims 28, 29, 31-48, and 55-58 have been amended to include an article in the preamble. Applicant respectfully requests withdrawal of this ground of rejection.

In addition, the Examiner finds Claims 28, 30-48, 57, and 58 indefinite because they are directed to a method or a process but do not recite any method or process steps. Claim 30 has been canceled. Claim 28, from which Claims 31-48, 57, and 58 depend, has been amended to recite the step of "inhibiting or eliminating the action of at least one cell cycle inhibitor." Applicant respectfully requests withdrawal of this ground of rejection.

The Examiner also finds Claim 49 and claims depending from it indefinite for a number of reasons: (1) the recitation "characterization in the it" is grammatically incorrect, (2) the phrase "the sensory cells of the inner ear" lacks antecedent basis, and (3) the recitation "in a position" is unclear. Finally, the Examiner finds Claim 55 indefinite because it is unclear whether the phrase "in an active quantity" is referring to the active ingredient or the cell cycle inhibitor. Claim 49 and claims depending therefrom have been canceled. Claim 55 has been

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amended to more clearly define that the active quantity refers to the active ingredient. Applicant respectfully requests withdrawal of this ground of rejection.

The Rejection of Claims Under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 29 and 30 have been rejected under 35 U.S.C. § 112, first paragraph, for lack of an enabling description in the Specification. The Examiner alleges lack of enablement with respect to (1) treatment of any disease or disorder of the inner ear linked with damage or destruction of the sensory cells by administering an inhibitor of a cell cycle inhibitor, and (2) preparation of a pharmaceutical composition or medicament. Claim 30 has been canceled. Applicant submits that the invention of Claim 29 is enabled by the application as filed in view of the knowledge of one skilled in the art at the time of filing. The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in a patent coupled with information known in the art without undue experimentation. A patent need not teach, and preferably omits, what is well known in the art. M.P.E.P. Section 2164.01. Applicant provides evidence below that one of ordinary skill in the art could practice the invention without undue experimentation at the time the application was filed.

a. The specification provides guidance on specific diseases or disorders and specific cell cycle inhibitors.

According to the Examiner, the Specification does not provide any guidance on what specific diseases or disorders can be treated or what specific cell cycle inhibitor can be targeted for inhibition. Applicant respectfully disagrees. The Specification explicitly provides guidance on specific diseases or disorders that can be treated according to the applicant's invention. Thus, the Specification defines that the disease or disorders that may be treated are those diseases and disorders of the inner ear that (a) are a cause of partial or complete hearing loss, and (b) are linked to damage to or destruction of sensory cells (*see, e.g.*, Specification, page 2, lines 28-35;

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page 4, lines 3-6). The Specification also provides guidance on specific cell cycle inhibitors to be targeted, namely, those cell inhibitors that are (a) present in the inner ear, and (b) are expressed in terminally differentiated cells to prevent reentry of these cells into the cell cycle (*see, e.g.*, Specification, page 3, lines 4-6; page 4, lines 7-14 and lines 24-29). In particular, the Specification describes cyclin-dependent kinase inhibitors, particularly $p21^{Cip1}$, $p27^{Kip1}$, and $p57^{Kip2}$ as suitable cell cycle inhibitors to be targeted (*see, e.g.*, Specification, page 4, lines 18-21). Therefore, applicant submits that the Specification provides adequate guidance on what specific diseases or disorders can be treated or what specific cell cycle inhibitor can be targeted for inhibition.

b. No undue experimentation is required to control the development of sensory cells by administering an inhibitor of cell cycle inhibitors.

The Examiner has relied on Pfister & Lowenheim (2002) *Gentherapeutische Aspecte am Innohr*, pp. 50-7, Lowenheim et al. (1999) *Proc. Natl. Acad. Sci. U.S.A.* 96:4084-8, and Chen & Segil (1999) *Development* 126:1581-90, to conclude that it would take undue experimentation to control the development of sensory cells by administering an inhibitor of cell cycle inhibitors. Specifically, the Examiner has cited a statement in Chen et al. that "the mechanisms that link developmental events to the cell cycle machinery that controls cell proliferation remain poorly understood." Applicant respectfully points out that Chen et al. also states that "$p27^{Kip1}$ provides a link between developmental control of cell proliferation and the morphological development of the inner ear" (Chen et al., Abstract). This is, in fact, the main finding of the experiments discussed in Chen et al. (*see* Chen et al., Title). Moreover, the Specification describes that genetic deletion of $p27^{Kip1}$ results in ongoing proliferation in the organ of Corti and new hair cell production (*see, e.g.*, Specification, page 8, line 16 to page 9, line 19). In $p27^{Kip1}$ heterozygous mice, new hair cell production can be stimulated by ototoxic injury to the cochlea

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(*see, e.g.*, Specification, page 9, lines 11-19). Thus, a reduction of $p27^{Kip1}$ levels to 50% of normal levels is sufficient to stimulate supporting cell proliferation and allow new hair cell production. These results indicate that cellular regeneration in supporting cells of the organ of Corti is blocked by the cyclin dependent kinase inhibitor $p27^{Kip1}$. These results clearly show the link between developmental control of cell proliferation and the morphological development of the inner ear. Moreover, these results show that inhibiting the function of $p27^{Kip1}$ results not only in supporting cell proliferation, but also in hair cell differentiation.

The Examiner also cites a statement in Pfister & Lowenheim that there is at present no therapeutic option available for hearing loss other than hearing aids. Applicant respectfully submits that this statement refers to the availability of clinical treatments for human patients. It generally takes years of clinical testing to obtain government approval for marketing a therapy for use in humans. However, clinical testing and government approval for a treatment is not a prerequisite for patentability. *See In re Brana*, 34 U.S.P.Q.2d 1436, 1142-3 (Fed. Cir. 1995) ("The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer. In view of all the foregoing, we conclude that applicant's disclosure complies with the requirements of 35 U.S.C. Section 112, paragraph 1."); *Scott v. Finney*, 32 U.S.P.Q.2d 1115, 1120 (Fed. Cir. 1994) ("Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings.").

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The Examiner states that there are no examples where an antisense gene therapy vector is delivered *in vivo* to treat any disease or disorders of the inner ear. The Examiner has relied on Agrawal & Kandimalla (2000) *Molec. Med. Today* 6:72-81, Branch (1998) *TIBS* 23:45-50, Green et al. (2000) *J. Am. Coll. Surg.* 191:93-105, and Jen & Gerwirtz (2000) *Stem Cells* 18:307-319, to conclude that the therapeutic use of antisense oligonucleotides was an unpredictable art at the time the invention was made. Applicant respectfully disagrees.

Contrary to the Examiner's assertion regarding lack of enablement, appended hereto as Attachment A is the Declaration of Dr. Jonathan Kil ("the Kil Declaration"), which describes experiments carried out by Dr. Kil and his co-workers demonstrating inhibition of $p27^{Kip1}$ function in supporting cells *in vivo* and *in vitro* using antisense oligonucleotides. Dr. Kil is the CEO of Sound Pharmaceuticals, Inc., the new owner of the above-identified patent application. A copy of his *curriculum vitae* is appended hereto as Attachment B and shows that he has been actively engaged in research on the inner ear pertaining to hearing loss for more than 10 years. As described in the Kil Declaration, by administering a $p27^{Kip1}$ antisense oligonucleotide to wild-type cochlear cultures treated with an ototoxic antibiotic, Dr. Kil and his colleagues showed a selective effect of $p27^{Kip1}$ antisense oligonucleotides on supporting cell proliferation in wild-type organ of Corti (*see* Kil Declaration, paragraph 5). They also demonstrated that $p27^{Kip1}$ antisense oligonucleotides locally delivered via microcatheter can induce cellular proliferation *in vivo* in the Guinea pig organ of Corti (*see* Kil Declaration, paragraph 6; Attachment C, FIGURE 1). In addition, Dr. Kil and his colleagues identified novel $p27^{Kip1}$ antisense oligonucleotides, such as a phosphothioate oligonucleotide, that are more effective than the prior art $p27^{Kip1}$ oligonucleotide at reducing $p27^{Kip1}$ mRNA and protein levels (*see* Kil Declaration, paragraphs 7 and 8; Attachment C, FIGURES 2-4). These results show that administration of $p27^{Kip1}$ antisense oligonucleotide induce cell proliferation, both *in vitro* in mouse cochlear

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cultures and *in vivo* in the organ of Corti. Applicant also points out that delivery of antisense oligonucleotides (*see, e.g.*, d'Aldin et al. (1998) *Brain. Res. Mol. Bran. Res.* 55(1):151-64 (Abstract) attached hereto as Attachment D; LeBlanc et al. (1999) *Hear. Res.* 135(1-2):105-12 (Abstract) attached hereto as Attachment E) and transgenes (*see, e.g.*, Wareing et al. (1999) *Hear. Res.* 128(1-2):61-9, attached hereto as Attachment F) to the cochlea of the ear has also been successfully accomplished by others in the field. Therefore, no undue experimentation is required to use antisense technology to inhibit the function of cell cycle inhibitors in the inner ear. In other sensory systems, such as the eye, antisense technology has already been used to treat a human disease or disorder. For example, the Federal Drug Administration (FDA) approved the human use of phosphothioate antisense oligonucleotides by intravitreal injection in CMV retinitis patients (Vitravene, Isis Pharmaceuticals) in 1998.

For all the reasons provided above, applicant submits that the invention of Claim 29 is supported by an enabling description in the Specification. Accordingly, applicant respectfully requests removal of this ground of rejection.

The Rejection of Claims Under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 28-61 have been rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that lacks an adequate written description in the Specification. According to the Examiner, the Specification does not provide the structure of any active ingredient encompassed by the claims. Specifically, the Examiner states that the Specification does not provide any structure for inhibitors of $p27^{Kip1}$, such as a sequence for an antisense inhibitor, an mRNA sequence by which an antisense sequence could be determined, or amino acid sequence or structural information for a peptide inhibitor of $p27^{Kip1}$, and no structural information for a small molecule inhibitor of $p27^{Kip1}$. The Examiner concludes that the Specification does not provide a detailed chemical structure or common structural characteristics of the active ingredients, such

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that one of skilled in the art would recognize that the inventor was in possession of the broad genus of active ingredients claimed at the time the application was filed. Applicant respectfully disagrees, for the reasons described below.

As an initial matter, Claims 30, 49-54, and 59-61 have been canceled. Applicant is claiming processes for the treatment or disorders of the inner ear using an active ingredient (Claims 28, 31-48, 57, and 58), methods of treating diseases or disorders of the inner ear using an active ingredient (Claim 29), and pharmaceutical compositions and medicaments comprising an active ingredient. Since the applicant is not claiming nucleic acid sequences (such as cDNA or antisense oligonucleotides) or amino acid sequences, the written description requirement may be met without disclosing specific amino acid or nucleic acid sequences.

Moreover, the Federal Circuit has recently clarified that "[i]t is incorrect ... that all functional descriptions of genetic material fail to meet the written description." *Enzo Biochem. Inc. v. Gen-Probe Inc.*, 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002). Thus, the written description requirement may be met by disclosure of functional characteristics when coupled with a known or disclosed correlation between function and structure. *Id.* The functional characteristics of the active ingredients used according to the applicant's invention are well-defined in the specification: The active ingredients used in the methods, processes, and pharmaceutical compositions of the invention are all defined by their ability to inhibit or eliminate the action of a cell cycle inhibitor present in the inner ear (*see, e.g.*, Specification, page 2, line 40 to page 3, line 11; page 4, lines 7-31). Furthermore, there are many known correlations between the function of inhibiting the action of a cell cycle inhibitors and structure. For example, the structures of inhibitors of the cell cycle inhibitor $p27^{Kip1}$ were known in the art at the time the application was filed, as described, for example, in Coats et al. (1996) *Science* 272:877-80 (appended hereto as Attachment G) and Hauser et al. (1997) *Cell Growth & Differentiation*

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8:203-11. Coats et al. discloses inhibition of $p27^{Kip1}$ function by antisense oligonucleotides that target base pairs 306 to 320 of murine $p27^{Kip1}$ (see Coats et al., page 879, Column 1, and footnote 14). Moreover, the Examiner has stated that Hauser et al. discloses protein and nucleic acid inhibitors of cell cycle inhibitors, such as antibodies to $p27^{Kip1}$ and $p27^{Kip1}$ antisense oligonucleotides (Examiner's Action, pages 13-14). Thus, one skilled in the art would appreciate that applicant had possession of the claimed invention at the time the application was filed. Accordingly, applicant respectfully requests withdrawal of this ground of rejection.

The Rejection of Claims Under 35 U.S.C. § 101

Claims 28, 31-48, 57, and 58 have been rejected under 35 U.S.C. § 101 as being improper process claims because they do not set forth any steps in the process. Claim 28, from which Claims 31-48, 57, and 58 depend, has been amended to recite the step of "inhibiting or eliminating the action of at least one cell cycle inhibitor." Applicant respectfully requests withdrawal of this ground of rejection.

Claims 49-53, 59, and 60 have been rejected under 35 U.S.C. § 101 as encompassing nonstatutory subject matter. Claims 49-53, 59, and 60 have been canceled. Therefore, this ground of rejection is now moot.

The Rejection of Claims Under 35 U.S.C. § 102(b)

Claims 49-56 and 59-61 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Hauser et al. (1997) *Cell Growth & Differentiation* 8:203-11. According to the Examiner, Hauser et al. discloses protein and nucleic acid inhibitors of cell cycle inhibitors. Claims 49-54 and 59-61 have been canceled. Claim 55, from which Claim 56 depends, is directed to a pharmaceutical composition or medicament comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one active ingredient able to inhibit or eliminate the action of a cell cycle inhibitor present in the inner ear. Applicant respectfully submits that

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Hauser et al. does not teach or suggest a pharmaceutical composition or medicament comprising a pharmaceutically acceptable carrier and an inhibitor of a cell cycle inhibitor. Therefore, Hauser et al. does not disclose or suggest every limitation of the invention claimed in Claims 55 and 56 and does not anticipate these claims. Accordingly, applicant respectfully requests withdrawal of this ground of rejection.

New Claim 62

New Claim 62 is directed to a process according to Claim 39, wherein the DNA molecule is an antisense DNA molecule. No new matter has been introduced. Support for Claim 62 can be found in the Specification, for example, at page 7, lines 32-35.

Other Matters

The Examiner has noted that no translation was provided for prior German Application No. 198 07 426.3. An English translation of parent international application PCT/EP99/01153, which is identical to parent German Application No. 198 07 426.3, is submitted herewith as Attachment H, together with a Declaration of the translator John Alfred Riches. Applicant respectfully requests that the above-identified application be accorded the February 23, 1998, priority date of German Application No. 198 07 426.3.

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CONCLUSION

In view of the above amendments, the foregoing remarks, and the Kil Declaration, applicant respectfully submits that all the pending claims are in condition for allowance. If any issues remain that may be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone applicant's attorney.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the U.S. Postal Service in a sealed envelope as first class mail with postage thereon fully prepaid and addressed to the U.S. Patent and Trademark Office, P.O. Box 2327, Arlington, VA 22202, on the below date.

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VERSION WITH MARKINGS TO SHOW CHANGES MADE MARCH 7, 2003

In the Claims

28. (Amended) A p[P]rocess for the treatment of diseases or disorders of the inner ear that are linked with damage or destruction of the sensory cells of the inner ear, [characterized in that for the regeneration of the sensory cells of the inner ear the inhibiting action of at least one cell cycle inhibitor present in the inner ear is at least partly inhibited or eliminated by an active ingredient] comprising the step of at least partly inhibiting or eliminating the action of at least one cell cycle inhibitor present in the inner ear using an active ingredient that promotes regeneration of the sensory cells of the inner ear.

29. (Amended) A m[M]ethod of treating diseases or disorders of the inner ear that are linked with damage or destruction of the sensory cells of the inner ear, comprising [by] administering an active ingredient that [able to] inhibits or eliminates the action of a cell cycle inhibitor present in the inner ear.

Claim 30 has been canceled.

31. (Amended) The p[P]rocess according to claim 28, characterized in that the regeneration of the sensory cells of the inner ear takes place by stimulating proliferation of the supporting cells of the inner ear.

32. (Amended) The p[P]rocess according to claim 28, characterized in that the sensory cells of the inner ear are hair [sensor] cells.

33. (Amended) The p[P]rocess according to claim 28, characterized in that cell cycle inhibitor is a cyclin-dependent kinase inhibitor.

34. (Amended) The p[P]rocess according to claim 33, characterized in that the cyclin-dependent kinase inhibitor is the cyclin-dependent kinase inhibitor $p27^{Kip1}$.

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35. (Amended) The p[P]rocess according to claim 28, characterized in that the disease or disorder of the inner ear is [a perceptive deafness] hearing loss.

36. (Amended) The p[P]rocess according to claim 28, characterized in that the active ingredient is at least one peptide or at least one protein.

37. (Amended) The p[P]rocess according to claim 28, characterized in that the active ingredient is at least one nucleic acid molecule.

38. (Amended) The p[P]rocess according to claim 37, characterized in that the nucleic acid molecule codes for a peptide or a protein.

39. (Amended) The p[P]rocess according to claim 37, characterized in that the nucleic acid molecule is a DNA molecule.

40. (Amended) The p[P]rocess according to claim 39, characterized in that the nucleic acid molecule is a cDNA molecule.

41. (Amended) The p[P]rocess according to claim 47, characterized in that the nucleic acid molecule is an RNA molecule.

42. (Amended) The p[P]rocess according to claim 28, characterized in that the active ingredient is in the form of a vector.

43. (Amended) The p[P]rocess according to claim 42, characterized in that the vector is a viral vector.

44. (Amended) The p[P]rocess according to claim 43, characterized in that the virus is a retrovirus, an adenovirus or an adeno-associated virus.

45. (Amended) The p[P]rocess according to claim 42, characterized in that the viral vector is a non-viral vector.

46. (Amended) The p[P]rocess according to claim 37, characterized in that [it] the active ingredient is a nucleic acid molecule packed in a liposome or lipoplex.

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47. (Amended) The p[P]rocess according to claim 28, characterized in that the active ingredient is used in a therapeutically active quantity.

48. (Amended) The p[P]rocess according to claim 28, characterized in that the active ingredient is intended for local application.

Claims 49-54 have been canceled.

55. (Amended) A p[P]harmaceutical composition or medicament, characterized in that it contains a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one active ingredient able to inhibit or eliminate the action of a cell cycle inhibitor present in the inner ear [in an active quantity and a pharmaceutically acceptable carrier].

56. (Amended) The p[P]harmaceutical composition or medicament of claim 55, characterized in that the active ingredient is [an active ingredient according to claim 50] a cyclin-dependent kinase inhibitor.

57. (Amended) The p[P]rocess according to claim 37 wherein said nucleic acid molecule is a recombinant [recombined] nucleic acid molecule.

58. (Amended) The p[P]rocess according to claim 42 wherein said vector carries a nucleic acid molecule.

Claims 59-61 have been canceled.

New Claim 62 has been added.

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